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         JUN 06
                 KOREAPAT updated with 41,000 documents
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         JUN 13
                 USPATFULL and USPAT2 updated with 11-character
                 patent numbers for U.S. applications
         JUN 19
                 CAS REGISTRY includes selected substances from
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                 web-based collections
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         JUN 25
                 CA/CAplus and USPAT databases updated with IPC
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         JUN 30
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         JUN 30 STN AnaVist enhanced with database content from EPFULL
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         JUL 28 CA/CAplus patent coverage enhanced
NEWS 18 JUL 28 EPFULL enhanced with additional legal status
                 information from the epoline Register
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         JUL 28 IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
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         AUG 25
                 CA/CAplus, CASREACT, and IFI and USPAT databases
                 enhanced for more flexible patent number searching
NEWS 26 AUG 27
                 CAS definition of basic patents expanded to ensure
                 comprehensive access to substance and sequence
                 information
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chain nodes :
10 11 20 21 22 23
ring nodes :
1 2 3 4 5 14 15 16 17 18 19 24
chain bonds :
2-18 4-10 10-11 15-20 20-21 20-22 22-23
ring bonds :
1-2 \quad 1-5 \quad 2-3 \quad 3-24 \quad 4-5 \quad 4-24 \quad 14-15 \quad 14-19 \quad 15-16 \quad 16-17 \quad 17-18 \quad 18-19
exact/norm bonds :
1-2 \quad 1-5 \quad 2-3 \quad 2-18 \quad 3-24 \quad 4-10 \quad 4-5 \quad 4-24 \quad 10-11 \quad 20-21 \quad 20-22 \quad 22-23
exact bonds :
15-20
normalized bonds :
14-15 14-19 15-16 16-17 17-18 18-19
isolated ring systems :
containing 1 :
```

G1:C,N

G2:Ak, NH2, NO2

G3:0

G4

G5:C, N, Zn, H

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:Atom

L1 STRUCTURE UPLOADED

=> d 11 L1 HAS NO ANSWERS L1 STR

G1 C, N

G2 Ak, NH2, NO2

G3 O

G4

G5 C, N, Zn, H

Structure attributes must be viewed using STN Express query preparation.

=> s 11 full

FULL SEARCH INITIATED 16:01:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE

100.0% PROCESSED 1679 ITERATIONS 113 ANSWERS SEARCH TIME: 00.00.01

L2 113 SEA SSS FUL L1

=> file caplus
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COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION TULL ESTIMATED COST 178.36 178.57

FILE 'CAPLUS' ENTERED AT 16:01:51 ON 15 SEP 2008
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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

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L3 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GΙ

PATENT NO.	KIND	DATE	APPLICAT	ION NO.	DATE						
WO 2008033747 WO 2008033747			WO 2007-U	JS77971	20070910						
	_ _		BA, BB, BG,	BH, BR, B	W, BY, BZ, CA,						
					E, EG, ES, FI,						
GB, GD,	GE, GH, GM	4, GT, HN,	HR, HU, ID,	IL, IN, I	S, JP, KE, KG,						
KM, KN,	KP, KR, KZ	Z, LA, LC,	LK, LR, LS,	LT, LU, L	Y, MA, MD, ME,						
MG, MK,	MN, MW, MX	K, MY, MZ,	NA, NG, NI,	NO, NZ, O	M, PG, PH, PL,						
PT, RO,	RS, RU, SC	C, SD, SE,	SG, SK, SL,	SM, SV, ST	Y, TJ, TM, TN,						
TR, TT,	TZ, UA, UG	G, US, UZ,	VC, VN, ZA,	ZM, ZW							
RW: AT, BE,	BG, CH, CY	Y, CZ, DE,	DK, EE, ES,	FI, FR, G	B, GR, HU, IE,						
IS, IT,	LT, LU, LV	/, MC, MT,	NL, PL, PT,	RO, SE, S	I, SK, TR, BF,						
BJ, CF,	CG, CI, CM	4, GA, GN,	GQ, GW, ML,	MR, NE, SI	N, TD, TG, BW,						
GH, GM,	KE, LS, MW	√, MZ, NA,	SD, SL, SZ,	TZ, UG, ZI	M, ZW, AM, AZ,						
BY, KG,	KZ, MD, RU	J, TJ, TM,	AP, EA, EP,	OA							
US 20080221132	A1	20080911	US 2007-8	352458	20070910						
PRIORITY APPLN. INFO.	:		US 2006-8	343590P	P 20060911						
			US 2007-8	395889P	P 20070320						
OTHER SOURCE(S):	MARPAT	MARPAT 148:355828									

$$C \equiv CH$$
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AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

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survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L3 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:351928 CAPLUS

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino)(phenyl)pyrrolo[2,3-d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT	KIN	D	DATE	APPLICATION NO.					DATE								
WO 2008	WO 2008033745					2008	0320	WO 2007-US77968						20070910			
W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	ΑZ,	ΒA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,	
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	GB,	GD,	GE,	GH,	GM,	GΤ,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	
	KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,	
	MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,	
	PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	
	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW					
RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	
	IS,	IT,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	
	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	
	GH,	GM,	KΕ,	LS,	MW,	MΖ,	NΑ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,	
	BY,	KG,	KΖ,	MD,	RU,	ТJ,	$_{ m TM}$										
US 2008	01613	320		A1		2008	0703		US 2	007-	8524	20070910					
PRIORITY APPLN. INFO.:								US 2	006-	8436	46P		P 2	0060	911		
									US 2	007-	8958	94P		P 2	0070.	320	
OTHER SOURCE(S): GI					PAT	148:	3558	14									

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

- AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = 0, S, NH, or alkylamino; Z = 0, S, NR1; Y = N or CR2; B = linker; D = C(0)NH2, NHC(S)CH3, CHC(0)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4- (chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of $\leq 0.1~(\mu M)$.
- IT 1011716-90-7P
 - RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L3 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

20070116			
CA, CH,			
GB, GD,			
KM, KN,			
MG, MK,			
PT, RO,			
TR, TT,			
HU, IE,			
BF, BJ,			
BW, GH,			
AZ, BY,			
20070116			
20060119			
070116			

OTHER SOURCE(S): MARPAT 147:211903

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$$R^{1}-NH$$
 N
 N
 R^{2}
 R^{3}
 R^{3}

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

Erich Leese

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

CRN 76-05-1 CMF C2 H F3 O2

IT 944739-19-9P 944739-25-7P 944739-27-9P 944739-36-0P 944739-42-8P 944739-65-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944739-19-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-25-7 CAPLUS

CN Carbamic acid, N-[(2E)-3-phenyl-1-[[4-[5-[[[(tetrahydro-2H-pyran-2-yl)oxy]amino]carbonyl]-2-pyrimidinyl]-1-piperazinyl]methyl]-2-propen-1-yl]-, 9H-fluoren-9-ylmethyl ester (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-27-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-36-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 2-A

RN 944739-42-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-65-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

4

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	PATENT NO.						KIND DATE				ICAT		DATE					
WO	2007	 J7082880				A1 20070726				WO 2	 007-:	EP50	20070116					
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		KG,	KΖ,	MD,	RU,	ΤJ,	TM											
ORIT	RITY APPLN. INFO.:			EP 2006-100571							71	A 20060119						
HER SO	DURCE	(S):			MAR	PAT	147:	2119	02									

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 N NH

 N NN

 N NN

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P

944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Syn

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

$$\begin{array}{c|c} & & & & \\ & & & \\ R & & & \\ \hline \end{array} \begin{array}{c} N & & \\ \hline \end{array} \begin{array}{c} C - NH - OH \\ \hline \\ \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

Erich Leese

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

Erich Leese

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

CM 2

CRN 76-05-1 CMF C2 H F3 O2

IT 944712-19-0P 944712-20-3P 944712-23-6P

944712-27-0P 944712-30-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-19-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 944712-20-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-23-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-27-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-30-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Absolute stereochemistry.

10/513699

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

DOCUMENT NUMBER: 144:192266

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V. SOURCE: PCT Int. Appl., 67 pp.

SOURCE: PCT Int. Appl., 67 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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OTHER SOURCE(5): CASREACT 144:192200; MARPAT 144:192200

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Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & CH = CH - CH - N & N & N \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

<12/04/2007>

Erich Leese

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$F - \begin{matrix} F \\ | \\ C - CO_2H \\ | \\ F \end{matrix}$$

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

IT 875138-54-8P 875138-59-3P 875138-62-8P

875138-66-2P 875138-70-8P 875138-73-1P

875138-77-5P 875138-78-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-54-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-59-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-62-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-methyl-3-phenyl-2-propen-1-yl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-66-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-70-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-73-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-77-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-78-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-77-5 CMF C28 H35 N5 O6

CM 2 CRN 144-62-7 CMF C2 H2 O4

L3 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.						D	DATE			APPL	ICAT	ION 1	NO.		D.						
	2005 2005								WO 2004-US31591 20040924												
	W:	CN,	CO,	CR,	CU,	CZ,	AU, DE, ID,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,				
		NO,	NZ,	OM,	PG,	PH,	LV, PL, TZ,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,				
	RW:	BW, AZ,	GH, BY,	GM, KG,	KE, KZ,	LS, MD,	MW, RU, GR,	MΖ, TJ,	NA, TM,	SD, AT,	SL, BE,	SZ, BG,	TZ, CH,	UG, CY,	ZM, CZ,	ZW, DE,	AM, DK,				
7) []	2004	SI, SN,	SK, TD,	TR, TG	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,				
CA	2539 1663	117			A1 20050407 A1 20050407 A1 20060607					CA 2	004-										
CN.		AT, IE,	BE, SI,	CH, LT,	DE, LV,	DK, FI,	ES, RO,	FR, MK,	GB, CY,	GR, AL,	IT, TR,	LI, BG,	LU, CZ,	NL, EE,	SE, HU,	MC, PL,	PT, SK,	HR			
JP US					T A1		2007 2008	0322 0605		CN 2004-80034571 JP 2006-528279 US 2006-574088						20040924					
	JP 2008094847 IORITY APPLN. INFO.:						2008	0424		US 2	003-	5058	-		20071030 P 20030924 P 20031229						
						US 2 JP 2	004- 006-	5610 5282	82P		P 20040409 A3 20040924										
HER SOURCE(S):					CASI	REAC	T 14	2:35								_ 5 _ 6					

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AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

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capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase) ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$C-NH-OH$$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT	NO.			KIN		DATE			APPL	ICAT	ION :	NO.		D	20040924 Z, CA, CH I, GB, GI R, KZ, LO IZ, NA, NI K, SL, SY A, ZM, ZV				
WO 2005	0307	04				2005	0407	;	——— WO 2	004-	 US31	 590		2	DATE 20040924 Z, CA, CH, GB, GD, R, KZ, LC, Z, NA, NI, K, SL, SY, A, ZM, ZW 4, ZW, AM, Z, DE, DK,				
W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,			
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,			
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,			
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	NΙ,			
	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,			
	ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW			
RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,			
	AZ,	BY,	KG,	KZ,	MD,	RU,	ΤJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,			
	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,			
		•	•	•		CF,	•	•		•		•		•	,				
	SN,	TD,	TG	•	·	,	·	·	•	•	,	~-	•	ŕ	,	·			
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									US 2	003-	5329	73P		P 2	0031	229			
									US 2										
									JP 2										
OTHER SOURCE	(S):			CAS	REAC	T 14	2:37							110 2	0010	<i>J</i>			

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

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capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase) ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$C-NH-OH$$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737757 CAPLUS

DOCUMENT NUMBER: 139:276911

TITLE: Preparation of N-(piperazinylmethyl-,

piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase

INVENTOR(S):
Van Emelen, Kristof

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA:	TENT	NO.			KINI	D	DATE			APP	LICAT	ION :	NO.		20030311 CA, CH, CN, GD, GE, GH, LC, LK, LR, NZ, OM, PH, TR, TT, TZ,					
WO	2003	 0764	 38											20030311						
	W:	CO, GM,	CR, HR,	CU, HU,	CZ, ID,	DE, IL,	DK, IN,	DM, IS,	DZ, JP,	EC KE	EE, KG,	ES, KP,	FI, KR,	GB, KZ,	GD, LC,	GE, LK,	GH, LR,			
		PL, UA,	PT, UG,	RO, US,	RU, UZ,	SC, VC,	SD, VN,	SE, YU,	SG, ZA,	SK ZM	SL, I, ZW	TJ,	TM,	TN,	TR,	TT,	TZ,			
	R₩:	KG, FI,	KZ, FR,	MD, GB,	RU, GR,	TJ, HU,	TM, IE,	AT, IT,	BE,	BG MC	, TZ, , CH,	CY, PT,	CZ, RO,	DE, SE,	DK, SI,	EE, SK,	ES, TR,			
CA	2475										, GW, 2003-									
EP	1485	378			A1	A1 20030918 CA 2003-2475766 A1 20030922 AU 2003-218735 A1 20041215 EP 2003-711979 B1 20080618								20030311 20030311						
EP		AT,	BE,	CH,	DE,	DK,	ES,	FR,			I, IT,						PT,			
BR CN	2003 1642					LV, FI, RO, MK, CY, AL, TR, BO A 20041221 BR 2003-760 A 20050720 CN 2003-805 T 20050908 JP 2003-574								20030311						
NZ	5348	33			A		2006	0728		NZ	2003-	5348	33	20030311						
AT	1010 3986 2836	15			A T B		2007 2008 2007	0715		ΑT	2007-10005212 20030311 2003-711979 20030311 2003-92105285 20030312									
IN	2004 2005	DN02	536 016		A A1		2007 2005	0413		TM	2004-	DM25	36		2	20030312 20040831 20040908				
ИО	MX 2004PA08795 NO 2004004135 JORITY APPLN. INFO.:						2004 2004			MX NO	2004- 2004- 2002-	PA87 4135	95		2 2	0040 0040	910 929			
										WO CN	2002- 2003-	EP14 8059	833 21							
סייוים מייוים	STIDAH	(0)			1 (T T)		100	0760	1 1											

OTHER SOURCE(S): MARPAT 139:276911

GI

$$\begin{array}{c|c}
R^2 \left[CH_2 \right]_{t} L - A \\
 & Z
\end{array}$$

AB The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH2; R1 = CONR3R4, NHCOR7, CO(alkanediyl)SR7, etc. (wherein R3, R4 = H, OH, alkyl, etc.; R7 = H, alkyl, alkylcarbonyl, etc.); R2 = H, OH, NH2, etc.; L = NR9CO, NR9SO2, NR9CH2 (R9 = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC50 of 7.723 against HDAC, was given.

IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} O \\ S - NH - CH_2 \\ O \\ Ph - CH_2 \\ \end{array}$$

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	PAT	CENT 1	NO.			KIN	D	DATE			APE	PLI	CAT	ION 1	NO.		Ι	DATE			
	WO	2003	 0764	 00		A1	_	2003	0918	WO 2003-EP2514							20030311				
		W:	ΑE,	AG,	AL,	AM,		AU,								BZ,	CA,	CH,	CN,		
			co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	ΕC	j,	EE,	ES,	FI,	GB,	GD,	GE,	GH,		
								IN,													
								MD,													
								SD,													
			UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZN	1,	ZW	·	·	·		·			
		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ	Ζ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	BY,		
								TM,													
								IE,													
			BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GÇ	2,	GW,	ML,	MR,	NE,	SN,	TD,	TG		
	CA	2475	764			A1		2003	0918					2475			2	20030	311		
	ΑU	2003	2187.	36		A1		2003	0922		ΑU	20	03-	2187.		20030311					
	ΕP	1485	353			A1		2004	1215		EP 2003-711980						2	20030	311		
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	۲,	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,		
			IE,	SI,	LT,	LV,	FΙ,	RO,	MK,	CY,	ΑI	J,	TR,	BG,	CZ,	EE,	HU,	SK			
		2003		81		А		2004				_		8081				20030	_		
	_	1639	_			А		2005	-		-			8056	-			20030	_		
		1642				Α		2005						8058				20030			
		5348				А		2005		NZ 2003-534834							20030311				
	JΡ	2005	5260	67				2005		JP 2003-574621							20030311				
		1010				Α		2007		CN 2007-10005212							20030311				
		2004				А		2007		IN 2004-DN2533							20040831				
		2005				A1		2005						5069	98			20040			
		2004				A		2005				_	-	7237				20040			
		2004				A		2005				_	-	7235				20040			
		2004				A		2005						7232				20040			
		2004				A		2005				_	-	7233				20040			
		2004				A		2005						7234				20040			
		2004				A A		2005						7236	0.0			20040			
		2004:				A		2004 2004						PA88	06			20040			
PRIOR						А		2004	1001					4194	a a b			20041001 20020313			
EKIOK]	AFF.	→ N1 →	TIALO	• •									EP14				20020			
																		20021			
											CIA	∠ 0	.05-	0009	4		110 Z	.0050) <u>1 1</u>		

WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GΙ

$$\begin{array}{c|c}
R^1 & Q = X & R^4 \\
 & & Z & C \\
 & & X \\
 & X \\
 & & X \\$$

AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

IT 603985-87-1P 603985-89-3P 603985-91-7P 603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-87-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 CMF C21 H23 N5 O4

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

<12/04/2007>

Erich Leese

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

$$CH_2-CH_2-N$$
 N
 $C-NH-OH$
 O

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2 10/513699

IT 603986-73-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603986-73-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(phenylmethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

3

REFERENCE COUNT:

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	TENT				KINI	D	DATE			APP:	LICAT	ION :	NO.		I	DATE				
											 2003-									
											, BG,						_			
											, EE,									
											, KG,									
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	, MW,	MX,	MΖ,	NO,	NΖ	, OM,	PH,			
		PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK	, SL,	ΤJ,	TM,	TN,	TR,	TT,	TZ,			
							VN,													
	RW:	GH,	GM,	ΚE,	LS,	MW,	MZ,	SD,	SL,	SZ	, TZ,	UG,	ZM,	ZW,	AM,	, AZ,	BY,			
											, СН,									
		FI,	FR,	GB,	GR,	HU,	ΙE,	ΙΤ,	LU,	MC.	, NL,	PT,	RO,	SE,	SI,	, SK,	TR,			
		BF,									, GW,									
CA	2476	065			A1		2003	0918		CA :	2003-	2476	065		4	20030311				
	2003				A1		2003	0922		AU :	2003-	2187	37		20030311					
AU	2003	2187	37		В2		2008	0410		EP 2003-711981 20030311										
EP	1485	099			AI		2004	1215								20030				
	R:										, IT,						PT,			
											, TR,			EE,						
	2003						2005				2003-					20030				
	1639						2005				2003-									
	1642				А		2005	0720			2003-									
JP	2005	5253	79		Т	20050825 JP 2003-574203 20050930 NZ 2003-534832 20070801 CN 2007-1000521: 20070112 IN 2004-DN2537 20050928 ZA 2004-7237								20030311						
	5348	_			A		2005	0930			2003-			20030311						
	1010		3		A		2007	0801		CN :	2007-	1000		20030311 20040831						
	2004		537		А		2007	0112												
	2004		37								2004-			4	20040	909				
	2004				A		2005				2004-			20040909						
	2004				A		2005				2004-									
	2004				A		2005				2004-									
	2004		-		A		2005				2004-					20040				
	2004				A		2005			'ΖΑ .	2004-	7236			4	20040				
MX	2004	PAU8	797		A		2004	1126			2004-					20040				
US	2004 2005 2004	0096	468		A1		2004	0505			2004-		85			20040				
					А		2004	0928			2004-		000			20040				
IORIT	Y APP	LN.	TNF.O	.:							2002-									
								2002-												
											2003-									
T					147 D.I		100	0610		WO .	2003-	£₽25	Т2		W 2	20030	311			

OTHER SOURCE(S): MARPAT 139:261308

GΙ

$$R^{1}$$
 $Q=X$ N $Z-R^{3}$ R^{4}

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases) 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

RN

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & \\ \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603992-32-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603992-32-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

ANSWER 11 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN T.3

1986:442843 CAPLUS ACCESSION NUMBER:

105:42843 DOCUMENT NUMBER: ORIGINAL REFERENCE NO.: 105:7101a,7104a

TITLE: Pyrimidinylpiperazines

Kihara, Noriaki; Ishida, Tatsukazu; Isayama, Shigeru; INVENTOR(S): Ishitoku, Takeshi; Tan, Hiroaki; Takahashi, Katsuya

PATENT ASSIGNEE(S): Mitsui Petrochemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 28 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61043173	A	19860301	JP 1984-163771	19840806
JP 05022702	В	19930330		
PRIORITY APPLN. INFO.:			JP 1984-163771	19840806
GI				

$$R^3$$
 COX NH NH $NC-NH_2$ $NC-NH_2$ $NC-NH_2$ $NC-NH_2$ $NC-NH_2$

AB The title compds. [I, R1 = H, substituted Me, alkoxycarbonyl; R2, R3 = H, substituted alkyl; X = alkoxy, OH, (substituted) NH2; n = 2, 3], useful as herbicides against common weeds (no data), were prepared Thus, the piperazinecarboxamidine derivative II sulfate reacted with MeOCH:C(COMe)CO2Me in MeOH/aqueous NaOH at room temperature overnight to give 88% I (R1 = PhCH2,

R2 = H, R3 = Me, X = OMe).

ΙT 102976-25-0P 102976-32-9P

> RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of, as herbicide)

102976-25-0 CAPLUS RN

5-Pyrimidinecarboxamide, 4-methyl-N-(phenylmethoxy)-2-[4-(phenylmethyl)-1-CN piperazinyl]- (CA INDEX NAME)

<12/04/2007>

RN 102976-32-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-methoxy-4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

=> file reg
COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 60.43 239.00

FULL ESTIMATED COST

SINCE FILE TOTAL

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

ENTRY SESSION
-8.80 -8.80

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FILE 'REGISTRY' ENTERED AT 16:02:33 ON 15 SEP 2008

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http://www.cas.org/support/stngen/stndoc/properties.html

=>

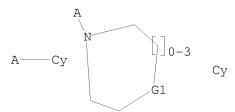
Uploading C:\Program Files\Stnexp\Queries\10506998jason.str

```
chain nodes :
1 2 4 11
ring nodes :
5 6 7 8 9 10
chain bonds :
1-4 5-11
ring bonds :
5-6 5-7 6-8 7-9 8-10 9-10
exact/norm bonds :
1-4 5-6 5-7 5-11 6-8 7-9 8-10 9-10
G1:C, N
Match level :
1:Atom 2:Atom 4:CLASS 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
Generic attributes :
1:
                     : Unsaturated
Saturation
Number of Carbon Atoms : less than 7
Type of Ring System : Monocyclic
Element Count :
Node 1: Limited
   C,C3-6
   N, N0-3
```

10/513699

L4 STRUCTURE UPLOADED

=> d 14 L4 HAS NO ANSWERS L4 STR



G1 C, N

Structure attributes must be viewed using STN Express query preparation.

=> Uploading C:\Program Files\Stnexp\Queries\10506998election.str

chain nodes :
19 32 34 45 46 47 56 57 58 60 61
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 20 21 22 23 24 25 26 27 28 29 30
31 39 40 41 42 43 44 49 50 52 53 54 55
chain bonds :

```
5-19 8-34 11-60 24-32 43-45 45-46 46-47 54-56 56-57 56-58 60-61
ring bonds :
1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 7-8 \quad 7-12 \quad 8-9 \quad 9-10 \quad 10-11 \quad 11-12 \quad 20-21 \quad 20-25
21 - 22 \quad 22 - 23 \quad 23 - 24 \quad 24 - 25 \quad 26 - 27 \quad 26 - 31 \quad 27 - 28 \quad 28 - 29 \quad 29 - 30 \quad 30 - 31 \quad 39 - 40 \quad 39 - 44 \quad 28 - 29 \quad 29 - 30 \quad 30 - 31 \quad 39 - 40 \quad 39 -
40-41 41-42 42-43 43-44 49-50 49-55 50-52 52-53 53-54 54-55
exact/norm bonds :
1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 5-19 \quad 7-8 \quad 7-12 \quad 8-9 \quad 8-34 \quad 9-10 \quad 10-11 \quad 11-12 \quad 11-60
  20-21 20-25 21-22 22-23 23-24 24-25 24-32 26-27 26-31 27-28 28-29 29-30
  30-31 39-40 39-44 40-41 41-42 42-43 43-44 43-45 45-46 46-47 49-50 49-55
  50-52 52-53 53-54 54-55 56-57 56-58 60-61
exact bonds :
54 - 56
isolated ring systems :
containing 1 : 7 : 20 : 26 : 39 : 49 :
G1:C,N
G2:Ak, NH2, NO2
G3:0
G4: [*1], [*2], [*3], [*4], [*5]
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 19:CLASS 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:CLASS 34:CLASS 39:Atom 40:Atom 41:Atom 42:Atom 43:Atom 44:Atom 45:CLASS 46:CLASS 47:CLASS 49:Atom
50:Atom 52:Atom 53:Atom 54:Atom 55:Atom 56:CLASS 57:CLASS 58:CLASS 60:CLASS
  61:Atom
L5
                  STRUCTURE UPLOADED
=> d 15
L5 HAS NO ANSWERS
L5
                                             STR
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *
Structure attributes must be viewed using STN Express query preparation.
=> s 15 full
FULL SEARCH INITIATED 16:04:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 596714 TO ITERATE
100.0% PROCESSED 596714 ITERATIONS
                                                                                                                                                                              10223 ANSWERS
SEARCH TIME: 00.00.08
L6
                           10223 SEA SSS FUL L5
=> file caplus
COST IN U.S. DOLLARS
                                                                                                                                            SINCE FILE TOTAL
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FULL ESTIMATED COST ENTRY SESSION 179.28 418.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL
ENTRY SESSION

CA SUBSCRIBER PRICE

0.00 -8.80

FILE 'CAPLUS' ENTERED AT 16:04:37 ON 15 SEP 2008
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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

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=> s 16 full L7 4042 L6

=> s 17 and py<2003 22958911 PY<2003

L8 2880 L7 AND PY<2003

=> file reg

COST IN U.S. DOLLARS

SINCE FILE TOTAL
ENTRY SESSION
3.56

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL

ENTRY SESSION
CA SUBSCRIBER PRICE 0.00 -8.80

FILE 'REGISTRY' ENTERED AT 16:06:14 ON 15 SEP 2008
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http://www.cas.org/support/stngen/stndoc/properties.html

=>

Uploading C:\Program Files\Stnexp\Queries\10506998three.str

```
chain nodes :
13 14 25 26 27 28 29 30
ring nodes :
1 2 3 4 5
              6 19 20 21 22 23
chain bonds :
2-23 5-13 13-14 20-25 25-26 25-27 27-28 27-29 28-30
ring bonds :
1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 19-20 \quad 19-24 \quad 20-21 \quad 21-22 \quad 22-23 \quad 23-24
exact/norm bonds :
1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-13 13-14 25-26 25-27 27-28
exact bonds :
20-25 27-29 28-30
normalized bonds :
19-20 19-24 20-21 21-22 22-23 23-24
isolated ring systems :
containing 1 :
```

G1:C,N

G2:Ak, NH2, NO2

G3:0

G4

G5:C,N,Zn,H

Match level:

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 13:CLASS 14:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS

L9 STRUCTURE UPLOADED

=> d 19

L9 HAS NO ANSWERS

L9 STR

G1 C, N

G2 Ak, NH2, NO2

G3 O

G4

G5 C, N, Zn, H

Structure attributes must be viewed using STN Express query preparation.

=> s 19 full

FULL SEARCH INITIATED 16:07:27 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 433 TO ITERATE

100.0% PROCESSED 433 ITERATIONS 112 ANSWERS

SEARCH TIME: 00.00.01

L10 112 SEA SSS FUL L9

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE TOTAL
ENTRY SESSION
178.82 600.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

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SINCE FILE TOTAL
ENTRY SESSION
-8.80

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Erich Leese

http://www.cas.org/legal/infopolicy.html

=> s 110 full L11 13 L10

=> d ibib abs hitstr tot

<12/04/2007>

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:556979 CAPLUS

DOCUMENT NUMBER: 148:538314

TITLE: Preparation of tricyclic hydroxamic acids as

inhibitors of histone deacetylase

INVENTOR(S): Shapiro, Gideon; Moncuso, John; Pierre, Tessier; Leit,

Silvana; Deziel, Robert; David, Smil; Richard,

Chesworth; Chantigny, Yves Andre; Patrick, Beaulieu

PATENT ASSIGNEE(S): Methygene Inc., Can.; En Vivo Pharmaceuticals, Inc.

SOURCE: PCT Int. Appl., 405pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	KIN:	KIND DATE APPLICATION NO.					. OV	DATE											
WO	WO 2008055068					A2 20080			1	wo 2	 007-1	JS82	 668	20071026					
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,		
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FΙ,		
		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,		
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,		
		MG,	MK,	MN,	MW,	MX,	MY,	MΖ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,		
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,		
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW						
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,		
		IS,	IT,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,		
		ΒJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML_{\prime}	MR,	NE,	SN,	TD,	ΤG,	BW,		
		GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,		
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM											
US	US 20080207590						2008	0828	1	US 2	007-	9251.	51		2	0071	026		
PRIORITY	PRIORITY APPLN. INFO.:								1	US 2	006-	8633	47P]	P 20061028				
									1	US 2	007-	8842	87P	P 20070110					
									1	US 2	007-	8842	87P]					

OTHER SOURCE(S): MARPAT 148:538314

GΙ

AB The title compds. I [Z = N(R1)OR2, H; L = a bond, N(OR2); when L = N(OR2), Z = H; when Z = H, L = N(OR2); R1, R2 = H, alkyl, aryl, etc.; J = a bond, :CH-, alkyl, alkyl(heteroalkyl)alkyl, etc.; Q = diazepine, pyrrolidine, diazabicyclo[3.3.1]nonane, etc.; B = dibenzo[b,f][1,4]oxazepine, benzo[b]pyrido[2,3-e][1,4]diazepine, benzo[f]thieno[2,3-b][1,4]oxazepine, etc.;], useful for the inhibition of histone deacetylase, were prepared E.g., a 3-step synthesis of II, starting from 10,11-

dihydrodibenz[b,f][1,4]oxazepin-11-one, was given. All exemplified compds. I have an IC50 of \leq 10 μM against one of more of HDAC-1 through HDAC-11 (data for representative compds. I were given). Pharmaceutical composition comprising the compound I and methods of treating polyglutamine (polyQ) expansion diseases such as Huntington's disease, are disclosed.

IT 1024007-45-1P 1024009-50-4P 1024009-80-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of tricyclic hydroxamic acids as inhibitors of histone deacetylase)

RN 1024007-45-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 1024009-50-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 1024009-80-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]hexahydro-1H-1,4-diazepin-1-yl]-N-hydroxy- (CA INDEX NAME)

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353109 CAPLUS

DOCUMENT NUMBER: 148:379651

TITLE: Pyrimidine derivatives as tyrosine kinase inhibitors

containing a zinc binding moiety and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

Curis, Inc., USA PATENT ASSIGNEE(S):

PCT Int. Appl., 81pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	ATENT	KIND DATE					APPL	ICAT		DATE								
W(2008 C	2008033746				_	2008	0320		WO 2	 007-	 US77		20070910				
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,	
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FI,	
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		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,	
		MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	ΝI,	NO,	NΖ,	OM,	PG,	PH,	PL,	
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW					
	RW:	ΑT,	BE,	ВG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙΤ,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	
		ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	
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		BY,	KG,	KΖ,	MD,	RU,	ТJ,	$_{ m IM}$										
U	US 20080125440						2008	0529		US 2	007-	8524	50		2	0070	910	
PRIORITY APPLN. INFO.:										US 2	006-	8437	30P		P 2	0060	911	
										US 2	007-	8959	01P		P 2	20070320		
OTHER SOURCE(S):						PAT	148:	3796.	51									

GI

The invention relates to tyrosine kinase inhibitors of formula I and II AB that contain a zinc-binding moiety and their use in the treatment of tyrosine related diseases and disorders such as cancer. The said derivs. may further act as HDAC inhibitors. Compds. of formula I and II wherein Cz is (un)substituted (hetero)aryl, and (un)substituted heterocyclic; Ar is (un)substituted (hetero)aryl; X3 is NH, alkylamino, O, and S; Z2 is O, S, NH and alkylamino; Y2 is N, CH, C-halo, C-(hetero)aryl, etc.; R21 is H and aliphatic; B is a liner. C is urea, thiourea, acetyl, thioacetyl, etc.; R8 is H, acyl, and (un)substituted aliphatic group; and their geometric isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, and solvates thereof, are claimed. Example compound III was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their tyrosine kinase inhibitory activity. ΙT 1012886-07-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as tyrosine kinase inhibitors containing a zinc binding moiety) ${\bf r}$

RN 1012886-07-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GΙ

PA.	PATENT NO.						DATE		-	APPL	ICAT		DATE					
	2008 2008		A2 20080320 A9 20080724			,	WO 2	007-	US77	20070910								
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		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,	
		MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NI,	NO,	NΖ,	OM,	PG,	PH,	PL,	
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW					
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙT,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	
		ΒJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	ΤG,	BW,	
		GH,	GM,	KΕ,	LS,	MW,	MZ,	NΑ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑP,	EA,	EP,	OA						
US	2008	0221	132		A1		2008	0911		US 2	007-	8524	58		2	0070	910	
PRIORIT	PRIORITY APPLN. INFO.:									US 2	006-	8435	90P		P 2	0060	911	
										US 2	007-	8958	89P		P 2	20070320		
OTHER SO	MAR:	PAT	148:	3558:	28													

$$C \equiv CH$$
 $C \equiv CH$
 $C \equiv CH$

AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other

functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P 1012886-07-5P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

RN 1012886-07-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

2008:351928 CAPLUS ACCESSION NUMBER:

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino) (phenyl) pyrrolo [2, 3d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	KIND DATE				APPL	ICAT		DATE									
WO	WO 2008033745				A2	_				 WO 2	007-		20070910				
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FΙ,
		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	ΗU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,
		MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW				
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,
		IS,	IT,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,
		ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,
		GH,	GM,	ΚE,	LS,	MW,	MZ,	ΝA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM									
US	US 20080161320						2008	0703		US 2	007-	8524	40		2	00709	910
PRIORITY APPLN. INFO.:									US 2	006-	8436	46P		P 2	00609	911	
										US 2	007-	8958	94P		P 20070320		
OTHER SOURCE(S):						PAT	148:	3558:	14								

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = 0, S, NH, or alkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of ≤ 0.1 (μ M).

ΙT 1011716-90-7P

> RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

20070116			
CA, CH,			
GB, GD,			
KM, KN,			
MG, MK,			
PT, RO,			
TR, TT,			
HU, IE,			
BF, BJ,			
BW, GH,			
AZ, BY,			
070116			
20060119			
20070116			

OTHER SOURCE(S): MARPAT 147:211903

GΙ

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

Erich Leese

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

10/513699

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	ATENT 1	KIN	D	DATE		APPLICATION NO.						DATE					
— W	0 2007	2007082880					2007	0726	;	WO 2	 007-:	EP50:	20070116				
	W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KN,
		KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,
		MN,	MW,	MX,	MY,	ΜZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW						
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,
		IS,	IT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ВJ,
		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	ΤG,	BW,	GH,
		GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,
		KG,	KΖ,	MD,	RU,	ΤJ,	TM										
PRIORI	PRIORITY APPLN. INFO.:									EP 2	006-	1005	71	i	A 2	0060	119
OTHER SOURCE(S):					MAR	PAT	147:	2119	02								
GI																	

$$R1$$
 OH OH NH

 N NH

 N NN

 N NN

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P

944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Syn

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

$$\begin{array}{c|c} & & & & \\ & & & \\ R & & & \\ \hline \end{array} \begin{array}{c} N & & \\ \hline \end{array} \begin{array}{c} C - NH - OH \\ \hline \\ \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

Erich Leese

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

Erich Leese

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:485854 CAPLUS

DOCUMENT NUMBER: 146:482095

Preparation of squaric acid derivatives as histone TITLE: deacetylase (HDAC) inhibitors for the treatment of

proliferative diseases

INVENTOR(S): Van Emelen, Kristof

Janssen Pharmaceutica N. V., Belg. PATENT ASSIGNEE(S):

SOURCE: PCT Int. Appl., 37pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA	TENT	NO.		KIN	D	DATE	E APPLICATION NO.							DATE				
WO	2007		A1	_	2007	0503	,				20061023							
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KΕ,	KG,	KM,	KN,	
		ΚP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,	
		MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	ΤT,	
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW							
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ΒJ,	
		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	GH,	
		GM,	KΕ,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,	BY,	
					RU,													
AU	2006	3079	18		A1		2007	0503		AU 2	006-		20061023					
	2623					2007	0503	1	CA 2	006-		20061023						
EP	1943	232			A1		2008	0716		EP 2	006-		2	0061	023			
	R:	ΑT,	BE,	ВG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙΤ,	LI,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	ΑL,	
		ΒA,	HR,	MK,	RS													
PRIORIT	PRIORITY APPLN. INFO.:								EP 2005-110080						A 20051027			
										WO 2	006-		W 20061023					
OTHER S	OURCE	MARPAT 146:482095																

GΙ

AB Title compds. I [wherein X = N or CH; R1, R2 = H, alkyl, Ph, etc.;] or N-oxides, pharmaceutically acceptable salts and stereoisomers thereof were prepared as histone deacetylase (HDAC) inhibitors. For instance, successive condensation of 3,4-diethoxy-3-cyclobutene-1,2-dione with 3-aminobiphenyl and 2-(1-piperazinyl)pyrimidine-5-carboxylic acid Et ester, ester hydrolysis, condensation of the resultant acid with NH2O-THP, and deprotection with TFA gave hydroxamic acid II. This compds. showed inhibition against HDAC with pIC50 = 7.7. The invented compds. are useful for the treatment of proliferative diseases.

IT 935670-93-2P 935670-95-4P 935670-97-6P 935670-99-8P 935671-01-5P 935671-03-7P 935671-05-9P 935671-07-1P 935671-09-3P 935671-11-7P 935671-13-9P 935671-15-1P 935671-17-3P 935671-19-5P 935671-21-9P 935671-23-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of squaric acid derivs. as histone deacetylase (HDAC) inhibitors for treatment of proliferative diseases)

RN 935670-93-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-([1,1'-biphenyl]-3-ylamino)-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935670-95-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[[1-(phenylmethyl)-3-pyrrolidinyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

RN 935670-97-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-(pentylamino)-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Me- (CH₂)₄-NH
$$C$$
-NH-OH

RN 935670-99-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-01-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[2-(3-chlorophenoxy)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-03-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[3-(diethylamino)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Erich Leese

<12/04/2007>

RN 935671-05-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[(2-furanylmethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-07-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[[1-(4-chlorophenyl)cyclopropyl]methyl]a mino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

RN 935671-09-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(3-pyridinylmethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-11-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenylethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-13-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[2-(2-pyridinyl)ethyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-15-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[[3-(trifluoromethyl)phenyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-17-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[(3,4,5-trimethoxyphenyl)methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

RN 935671-19-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[2-(phenylamino)ethyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-21-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 935671-23-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenoxyethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

<12/04/2007>

Erich Leese

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

DOCUMENT NUMBER: 144:192266

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S):

Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., I

SOURCE: PCT Int. Appl., 67 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	PATENT NO.										ICAT									
	2006	49		A2 20060202							20050725									
WO	2006010749				A3		2006	0608												
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		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,			
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KP,	KR,	KΖ,			
		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	ΜZ,	NA,			
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		SL,	SM,	SY,	ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	YU,			
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		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	ΤG,	BW,	GH,			
		GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,			
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THER SO	OURCE	(S):			CASREACT 144:192266; MARPAT 144:192266															

OTHER SOURCE(5): CASREACT 144:192200; MARPAT 144:192200

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Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & CH = CH - CH - N & N & N \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

<12/04/2007>

Erich Leese

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

Moradei, Oscar; Paquin, Isabelle; Leit, Silvana; INVENTOR(S):

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.					KIND DATE				APPL									
WO	2005	0307	05		A1		2005	0407								0040	924	
WO	2005																	
	W:	•	•		•			AZ,				•	•					
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,	
			,	,	,	,	,	IL,	,		,	•	,	,	,	,	,	
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	${ m MZ}$,	NΑ,	NΙ,	
		NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
		ТJ,	TM,	TN,	TR,	TΤ,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW	
	RW:	BW,	GH,	GM,	KΕ,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	
		ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	
		EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	ΙΤ,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	
		SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML ,	MR,	ΝE,	
		SN,	TD,	ΤG														
AU 2004276337			A1		2005	0407	,	AU 2	004-	2763								
														20040924				
EP	1663	953			A1		2006	0607		EP 2	004-	7890	74		2	0040	924	
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,	
		ΙE,	SI,	LT,	LV,	FI,	RO,	MK,	CY,	AL,	TR,	BG,	CZ,	EE,	HU,	PL,	SK,	F
CN	1882	529			A		2006	1220		CN 2	004-		20040924					
JP	2007	5067	85		T		2007	0322		JP 2	006-	5282		20040924 20060323				
US	2008	0132	459		A1		2008	0605		US 2	006-	5740		20060323				
JP	2008	0948	47		A		2008	0424		JP 2	007-	2813		20071030				
ORITY APPLN. INFO.:									US 2	003-	5058	84P		P 2	0030	924		
										US 2								
										US 2	004-	5610	82P		P 2	0040	409	
										JP 2								
										WO 2	004-	US31	591		W 2	0040	924	
ER SO	DURCE	(S):			CAS	REAC	T 14	2:35	5054	; MA	RPAT	142	:355	054				

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AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-82-6P 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

RN 603985-82-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-86-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$HO-CH_2$$
 O
 CH_2-N
 N
 $C-NH-OH$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX

NAME)

$$C-NH-OH$$

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OF \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATE	KIN	D																	
WO 2	WO 2005030704						2005		WO 2004-US31590										
Ţ	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,		
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,		
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KP,	KR,	KΖ,	LC,		
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,		
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,		
		ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW		
]	RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,		
		AΖ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,		
		EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,		
		SI,	SK,	TR,	BF,	ΒJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,		
		SN,	TD,	ΤG															
JP 2	0080	948	47		Α		2008	0424		JP 2	007-		20071030						
PRIORITY A	APPI	N.	INFO	.:						US 2	003-		P 2	0030	924				
										US 2003-532973P						P 20031229			
										US 2	004-	5610	82P		P 2	0040	409		
										JP 2	006-	5282	79		A3 2	0040	924		
OTHER SOU	CASREACT 142:373563; MARPAT 142:373563																		

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

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capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-82-6P 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

RN 603985-82-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-86-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$HO-CH_2$$
 O
 CH_2-N
 N
 $C-NH-OH$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX

NAME)

$$C-NH-OH$$

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OF \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737757 CAPLUS

DOCUMENT NUMBER: 139:276911

TITLE: Preparation of N-(piperazinylmethyl-,

piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase

INVENTOR(S):
Van Emelen, Kristof

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA:	TENT	NO.			KIND DATE					APP	LICAT	ION :	DATE						
WO	2003	0764	38								2003-					0030	311		
	W:	CO, GM,	CR, HR,	CU, HU,	CZ, ID,	DE, IL,	DK, IN,	DM, IS,	DZ, JP,	EC KE	B, BG, E, EE, E, KG, I, MW,	ES, KP,	FI, KR,	GB, KZ,	GD, LC,	GE, LK,	GH, LR,		
		PL, UA,	PT, UG,	RO, US,	RU, UZ,	SC, VC,	SD, VN,	SE, YU,	SG, ZA,	SK ZM	I, SL, I, ZW	TJ,	TM,	TN,	TR,	TT,	TZ,		
	R₩:	KG, FI,	KZ, FR,	MD, GB,	RU, GR,	TJ, HU,	TM, IE,	AT, IT,	BE,	BG MC	TZ, G, CH,	CY, PT,	CZ, RO,	DE, SE,	DK, SI,	EE, SK,	ES, TR,		
CA	2475										9, GW, 2003-								
EP	1485	378			A1		2004	1215		AU EP	2003- 2003-	2187 7119		20030311 20030311 20030311					
EP	1485 R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,			I, IT,						PT,		
BR CN	2003 1642 2005							1221	·	BR	2003-	7606	·	·	2	0030	311 311		
NZ	5348	33			A		2006	0728		NZ	2003-	5348	33		2003031 2003031 2003031				
AT	1010 3986 2836	15			A T B		2007 2008 2007	0715		ΑT	2003-	7119		20030311 20030311 20030312					
IN	2004 2005	DN02	536 016		A A1		2007 2005	0413		TNT	2004-	DM25		20040831 20040908					
		0041	795 35		A 20041126 A 20040929					MX NO	2004- 2004-	PA87 4135	95	20040910 20040929 P 20020313					
								WO CN	2002- 2003- 2003-	EP14 8059	833 21		A 2 A3 2	0021	223 311				
סייוים מייוים	STIDOR	101			NANDI	D 20 CF	120.	2760	1 1										

OTHER SOURCE(S): MARPAT 139:276911

GI

$$\begin{array}{c|c}
R^2 \left[CH_2 \right]_{t} L - A \\
 & Z
\end{array}$$

AB The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH2; R1 = CONR3R4, NHCOR7, CO(alkanediyl)SR7, etc. (wherein R3, R4 = H, OH, alkyl, etc.; R7 = H, alkyl, alkylcarbonyl, etc.); R2 = H, OH, NH2, etc.; L = NR9CO, NR9SO2, NR9CH2 (R9 = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC50 of 7.723 against HDAC, was given.

IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} O \\ S - NH - CH_2 \\ O \\ Ph - CH_2 \\ \end{array}$$

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	PAT					KIN:				APPLICATION NO.							DATE		
	WO										WO :	 2003-	 EP25	${14}$		2	 0030	311	
		W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB	, BG,	BR,	BY,	BΖ,	CA,	CH,	CN,	
			CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC	, EE,	ES,	FI,	GB,	GD,	GE,	GH,	
			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	, KG,	KP,	KR,	KΖ,	LC,	LK,	LR,	
			LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	, MW,	MX,	MZ,	NO,	NZ,	OM,	PH,	
												, SL,							
			UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM	, ZW							
		RW:	GH,	GM,	ΚE,	LS,	MW,	MZ,	SD,	SL,	SZ	, TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,	
			KG,	KΖ,	MD,	RU,	TJ,	TM,	AT,	BE,	BG	, СН,	CY,	CZ,	DE,	DK,	EE,	ES,	
			FΙ,	FR,	GB,	GR,	HU,	IE,	IT,	LU,	MC	, NL,	PT,	RO,	SE,	SI,	SK,	TR,	
												, GW,							
	CA	2475	764			A1		2003	0918		CA :	2003-							
	AU	2003	2187	36		A1		2003	0922		AU :	2003-	2187	36		2003031			
	ΕP	1485	353			A1		2004	1215		EP :	2003-		2	0030	311			
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT,	LI,	LU,	NL,	SE,	MC,	PT,	
			ΙE,	SI,	LT,	LV,	FI,	RO,	MK,	CY,	AL	, TR,	BG,	CZ,	EE,	HU,	SK		
	BR	2003	0800	-				2004	1221			2003-					0030	311	
	CN	1639	125			А		2005	0713		CN :	2003-	8056	75		2	0030	311	
	CN	1642	551			Α		2005	0720		CN :	2003-	8058	33		2	0030	311	
	NZ	5348	34			Α		2005	0729		NZ :	2003-							
	JΡ	2005	5260	67		Τ		2005	0902			2003-		20030311					
	CN	1010	0780	3		A 2005072 A 2005072 T 2005090 A 2007080					CN :	2007-	1000						
	ΙN	2004	DN02	533		Α		2007		IN :	2004-		2	0040	831				
	US	2005	0107	384				2005	0519		US :	2004-	5069	98		2	0040	908	
		2004				А		2005			ZA :	2004-	7237			2	0040		
		2004				А		2005			ZA :	2004-	7235			2	0040		
		2004				Α		2005			ZA :	2004-	7232			2	0040		
	ZA	2004	0072	33		А		2005								2	0040		
		2004				А		2005		6 ZA 2004-7234						2	0040		
		2004				Α		2005								2	0040		
		2004				А		2004			MX :	2004-	PA88	06		2	0040		
		2004				А		2004	1001			2004-					0041		
PRIOR	CTIS	APP:	.:							2002-									
												2002-					0021		
											CN :	2003-	8059	21		A3 2	0030	311	

WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GΙ

$$\begin{array}{c|c}
R^1 & Q = X & R^4 \\
 & & Z & C \\
 & & X \\
 & X \\
 & & X \\$$

AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

IT 603985-83-7P 603985-87-1P 603985-89-3P 603985-91-7P 603985-95-1P

0000000 01 /1 000000 00 11

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-83-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (10:9) (CA INDEX NAME)

CM 1

CRN 603985-82-6 CMF C24 H28 N6 O4 S

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-87-1 CAPLUS

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 CMF C21 H23 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

Erich Leese

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA'	TENT	NO.			KIND DATE					APPL	ICAT		DATE				
	R₩:	AE, CO, GM, LS, PL, UA, GH, KG, FI, BF,	AG, CR, HR, LT, PT, UG, GM, KZ, FR,	CU, HU, LU, RO, US, KE, MD, GB,	A1 AM, CZ, ID, LV, RU, UZ, LS, RU, GR, CG,	AT, DE, IL, MA, SC, VC, MW, TJ, HU, CI,	DK, IN, MD, SD, VN, MZ, TM, IE, CM,	AZ, DM, IS, MG, SE, YU, SD, AT, IT, GA,	BA, DZ, JP, MK, SG, ZA, SL, BE, LU, GN,	BB, EC, KE, MN, SK, ZM, SZ, BG, MC, GQ,	EE, KG, MW, SL, ZW TZ, CH, NL, GW,	BR, ES, KP, MX, TJ, UG, CY, PT, ML,	BY, FI, KR, MZ, TM, CZ, RO, MR,	GB, KZ, NO, TN, ZW, DE, SE,	CA, GD, LC, NZ, TR, AM, DK, SI, SN,	O030 CH, GE, LK, OM, TT, AZ, EE, SK, TD,	CN, GH, LR, PH, TZ, BY, ES, TR,
_	2476				A1		2003				003-					0030	-
	2003				A1		2003			AU 2	003-	2187	37		2	0030	311
	2003		-		B2		2008				000	7110	0.1		^		211
EP	1485 R:				A1		2004 EC				003-					0030 MC,	
CN	2003 1639	IE, 0076 125	SI, 24	LT,	LV, A A	FI,	RO, 2005 2005	MK, 0111 0713	CY,	AL, BR 2 CN 2	TR, 003- 003-	BG, 7624 8056	CZ, 75		НU, 2 2	SK 0030 0030	311 311
	1642				A		2005	0720			003-					0030	
_	2005		79				2005			-	003-				_	0030	
	5348	_	_		А		2005				003-					0030	
	1010				A		2007				007-					0030	
	2004				A		2007				004-					0040	
	2004				A		2005				004-					0040	
	2004				A A		2005				004-					0040	
	2004				A A		2005 2005				004 - 004 -					0040	
	2004				A		2005				004-					0040	
	2004				A		2005				004-					0040	
	2004				A		2003				004-		97			0040	
	2005		-		A1		2005	_			004-		-			0040	
	2003				A		2003				004-		0.5			0040	
	RIORITY APPLN. INFO.:						2001	0320		US 2 WO 2 CN 2	002- 002- 003-	3637 EP14 8059	833 21		P 2 A 2 A3 2	0020 0021 0030	313 223 311
OTHED C	OLID CE	(C).			MADI	ידי ער כ	120.	0610		wo 2	003-	LP25	ТЭ		W 2	0030	311

OTHER SOURCE(S): MARPAT 139:261308

<12/04/2007>

GΙ

$$R^{1}$$
 $Q=X$ N $Z-R^{3}$ R^{4}

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases) 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

RN

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file erg

'ERG' IS NOT A VALID FILE NAME

SESSION CONTINUES IN FILE 'CAPLUS'

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.40	-19.20

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STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3 DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

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<12/04/2007>

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chain nodes :
10 11 20 21 22 23 24 25 27 28 29 30 31 32 33 34 35
ring nodes :
1 2 3 4 5 14 15 16 17 18 19 26
chain bonds :
1-27 \quad 1-28 \quad 2-18 \quad 3-33 \quad 3-34 \quad 4-10 \quad 5-29 \quad 5-30 \quad 10-11 \quad 15-20 \quad 16-35 \quad 20-21 \quad 20-22
22-23 22-24 23-25 26-31 26-32
ring bonds :
1-2 1-5 2-3 3-26 4-5 4-26 14-15 14-19 15-16 16-17 17-18 18-19
exact/norm bonds :
1-2 \quad 1-5 \quad 2-3 \quad 2-18 \quad 3-26 \quad 4-10 \quad 4-5 \quad 4-26 \quad 10-11 \quad 20-21 \quad 20-22 \quad 22-23
exact bonds :
1-27 \quad 1-28 \quad 3-33 \quad 3-34 \quad 5-29 \quad 5-30 \quad 15-20 \quad 16-35 \quad 22-24 \quad 23-25 \quad 26-31 \quad 26-32
normalized bonds :
14-15 14-19 15-16 16-17 17-18 18-19
isolated ring systems :
containing 1 :
G1:C,N
G2:Ak, NH2, NO2
G3:0
G4
G5:C,N,Zn,H
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom
16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS
24:CLASS 25:CLASS 26:Atom 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 35:CLASS
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L12 STRUCTURE UPLOADED

=> d 112 L12 HAS NO ANSWERS L12 STR

Structure attributes must be viewed using STN Express query preparation.

=> s 112 full

FULL SEARCH INITIATED 16:08:56 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE

100.0% PROCESSED 1679 ITERATIONS 89 ANSWERS

SEARCH TIME: 00.00.01

L13 89 SEA SSS FUL L12

=> file caplus COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION 850.81 FULL ESTIMATED COST 178.82 DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL ENTRY SESSION CA SUBSCRIBER PRICE -19.200.00

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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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=> s 113 full L14 9 L13

=> d ibib abs hitstr tot

<12/04/2007>

L14 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	CENT :	NO.			KIN	D	DATE			APPL	ICAT		DATE					
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	R₩:	TR, AT, IS, BJ, GH,	TT, BE, IT, CF, GM,	TZ, BG, LT, CG, KE,	UA, CH, LU, CI, LS,	UG, CY, LV, CM, MW,	US, CZ, MC, GA, MZ,	UZ, DE, MT, GN, NA,	VC, DK, NL, GQ, SD,	VN, EE, PL, GW, SL,	ZA, ES, PT, ML, SZ,	ZM, FI, RO, MR, TZ,	ZW FR, SE, NE,	GB, SI, SN,	GR, SK, TD,	HU, TR, TG,	IE, BF, BW,	
PRIORITY	US 20080221132 RIORITY APPLN. INFO.:						2008			US 2 US 2 US 2	006-	8435	_	20070910 P 20060911 P 20070320				

$$A-B-C$$
 I MeO N II

AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:351928 CAPLUS

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino) (phenyl) pyrrolo [2, 3d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA'	TENT :	NO.			KIND DATE				APPLICATION NO.							DATE			
WO	2008	45		A2		20080320			 WO 2	007-	 US77	968		20070910					
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	GB, GD, GE,			GE,	GH,	GM,	GΤ,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,		
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,		
	MG, MK, MN,				MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,		
	PT, RO, RS,				RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,		
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		GH,	GM,	ΚE,	LS,	MW,	MΖ,	ΝA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,		
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM											
US	US 20080161320						2008	0703		US 2	007-	8524	40		2	0070	910		
PRIORITY APPLN. INFO.:										US 2	006-	8436	46P		P 2	0060	911		
										US 2	007-	8958	94P		P 2	0070	320		
OTHER S		MAR	PAT	148:	3558:	14													

OTHER SOURCE(S): MARPAT 148:355814

GΙ

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = O, S, NH, or alkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un) substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of ≤ 0.1 (μM).

ΙT 1011716-90-7P

> RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

TENT	NO.			KIND DATE				1	APPL:		DATE 						
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KP, KR,				LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,	
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RS, RU, S				SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,	
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KG, KZ, MI				RU,	ΤJ,	TM											
CA 2630717					A1 20070726				CA 2007-2630717						20070116		
RIORITY APPLN. INFO.:								EP 2006-100570						A 20060119			
								WO 2007-EP50371						W 2	0070	116	
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INFO.: EP 2006-1005	2007082874 A1 20070726 WO 2007-EP50371 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, KG, KZ, MD, RU, TJ, TM 2630717 Y APPLN. INFO:: CA 2007-2630717 EP 2006-100570 WO 2007-EP50371	2007082874 A1 20070726 WO 2007-EP50371 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, KG, KZ, MD, RU, TJ, TM 2630717 A1 20070726 CA 2007-2630717 Y APPLN. INFO:: EP 2006-100570 WO 2007-EP50371	2007082874 A1 20070726 W0 2007-EP50371 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, KG, KZ, MD, RU, TJ, TM 2630717 A1 20070726 CA 2007-2630717 Y APPLN. INFO:: EP 2006-100570 A 2 WO 2007-EP50371 W 2	2007082874 A1 20070726 W0 2007-EP50371 20070 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, KG, KZ, MD, RU, TJ, TM 20070 20070 20070 20070 20070 20070	

OTHER SOURCE(S): MARPAT 147:211903

GΙ

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

Erich Leese

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

10/513699

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATE	KIND DATE			APPLICATION NO.						DATE							
WO 2	WO 2007082880						20070726		;	wo 2	 007-:	EP50:	 379		20070116		
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KN,
	KP, KR, KZ,				LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,
	MN, MW, MX,					MZ,	NA,	NG,	NI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,
	RS, RU, SC,					SE,	SG,	SK,	SL,	SM,	SV,	SY,	IJ,	TM.	TN,	TR,	TT,
							VC,					·	·	·	·	·	·
	RW:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,
							MC,										
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PRIORITY	- ,	- ,			EP 2006-100571						A 20060119						
OTHER SOURCE(S):					MARPAT 147:211902												
GI																	

$$R1$$
 OH OH NH

 N NH

 N NN

 N NN

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P

944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Syn

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

Erich Leese

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

Erich Leese

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ &$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

144:192266 DOCUMENT NUMBER:

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent English LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA'							KIND DATE			APPLICATION NO.						DATE			
	2006 2006				A2		2006		WO 2005-EP53611					20050725					
	₩:	CN, GE, LC,	CO, GH, LK,	CR, GM, LR,	CU, HR, LS,	CZ, HU, LT,	DE, ID, LU,	DK, IL, LV,	DM, IN, MA,	DZ IS MD	, BG, , EC, , JP, , MG,	EE, KE, MK,	EG, KG, MN,	ES, KM, MW,	FI, KP, MX,	GB, KR, MZ,	GD, KZ, NA,		
		SL,		SY,							, RO, , UA,								
	RW:	IS, CF,	IT, CG,	LT, CI,	LU, CM,	LV, GA,	MC, GN,	NL, GQ,	PL, GW,	PT. ML.	, ES, , RO, , MR,	SE, NE,	SI, SN,	SK, TD,	TR, TG,	BF, BW,	BJ, GH,		
ΙΙΑ	2005	KG,	KΖ,	MD,	RU,	ΤJ,	TM	·	ŕ	·	, 12, 2005-:	·	r	·	·	АД, 0050	ŕ		
CA					A1 20060202			CA 2005-2572971 EP 2005-777776											
		AT, IS,	BE,	BG, LI,	CH, LT,	CY,	CZ,	DE,	DK,	EE,	, ES, , PT,	FI,	FR,	GB,	GR,	HU,	ΙE,		
CN	1993																		
BR	CN 1993356 JP 2008508234 BR 2005013891 KR 2007043978					T 20080321 A 20080520 A 20070426				JP 2007-523072 BR 2005-13891 KR 2007-701641					20050725				
IN	US 20070135424 IN 2007DN00658 MX 200701119						20070614 20070803 20070315			US 2007-626215 IN 2007-DN658 MX 2007-1119					20070123				
NO	NO 2007001117 IORITY APPLN. INFO.:				A		2007			NO 2 EP 2 US 2	2007-: 2004-: 2004-:	1117 7717 5923	1 57P]	2 A 2 P 2	0070 0040 0040	227 728 729		
OTHER S	OURCE	(S):			WO 2005-EP53611 W 20050725 CASREACT 144:192266; MARPAT 144:192266														

OTHER SOURCE(S): CASREACT 144:192266; MARPAT 144:192266

GΙ

Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & CH = CH - CH - N & N & N \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

<12/04/2007>

Erich Leese

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$${\scriptstyle F-C-CO_2H\atop \mid\atop F}$$

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

$$\begin{array}{c|c} \mathsf{O} & \mathsf{CH}_2\mathsf{-}\mathsf{OMe} \\ \mathsf{N} & \mathsf{N} & \mathsf{CH}\mathsf{-}\mathsf{CH} = \mathsf{CH} \end{array}$$

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

L14 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

					APPLICATION NO.							DATE						
WO	2005	0307	05	A1				0050407		WO 2004-US31591								
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
								DK,										
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,	
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	ΝI,	
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
		ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW	
	RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	
		ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	
					•	•	•	HU,			•	•	•					
		SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	
		,	TD,															
	AU 2004276337																	
_	CA 2539117									CA 2004-2539117								
EP	EP 1663953								EP 2004-789074									
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									JP 2006-528279									
														20060323				
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												5282	-					
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OTHER SO	OURCE	(S):			CAS!	REAC	Т 14	Z : 35.	5054	; MA	KPAT	142	:355	054				

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase) ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$C-NH-OH$$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

6

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

	PATENT NO.					KIND DATE				APPLICATION NO.						DATE		
	WO 2005030704				A1	_	20050407											
		W:	ΑE,	AG,	AL,	ΑM,	ΑT,	AU,	AZ,	BA,	BB,	ВG,	BR,	BW,	BY,	ΒZ,	CA,	CH,
			CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,
			GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KΕ,	KG,	KP,	KR,	KΖ,	LC,
			LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	NI,
			NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
			ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
		RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,
			ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,
			EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,
			SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,
			SN,	TD,	TG													
	JΡ	2008	0948	47		Α		2008	0424	JP 2007-281356						20071030		
PRIOR	RITY	APP	LN.	INFO	.:						US 2	003-	5058	84P		P 2	0030	924
											US 2	003-	5329	73P		P 2	0031	229
											US 2	004-	5610	82P		P 2	0040	409
											JP 2	006-	5282	79		A3 2	0040	924
OTHER						CAS	REAC	T 14	2:37	3563	; MA	RPAT	142	:373	563			

GΙ

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20 μM . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase) ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$C-NH-OH$$

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

6

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	PAT	CENT 1	NO.			KIND DATE				APPLICATION NO.						DATE				
	WO	2003	 0764	 00		A1 200309			0918	WO 2003-EP2514							20030311			
		W:	ΑE,	AG,	AL,	AM,		AU,								BZ,	CA,	CH,	CN,	
			co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	ΕC	j,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	
								IN,												
								MD,												
								SD,												
			UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZN	1,	ZW	·	·	·		·		
		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ	Ζ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	BY,	
								TM,												
								IE,												
			BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GÇ	2,	GW,	ML,	MR,	NE,	SN,	TD,	TG	
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	ΑU	2003	2187.	36		A1 20030922				AU 2003-218736						20030311				
	ΕP	1485353			A1		2004	1215	EP 2003-711980					20030311						
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	۲,	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,	
			IE,	SI,	LT,	LV,	FΙ,	RO,	MK,	CY,	ΑI	J,	TR,	BG,	CZ,	EE,	HU,	SK		
		2003		81		А		2004				_		8081				20030	_	
	_	1639	_			А		2005	-		-			8056	-			20030	_	
		1642				A 20050720											20030			
		5348				A 20050729				NZ 2003-534834						20030311				
	JΡ	2005	5260	67		T 20050902				JP 2003-574621						20030311				
		1010				A 20070801				CN 2007-10005212							20030311			
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		2005				A1 20050519				US 2004-506998							20040			
		2004				A		2005				_	-	7237				20040		
		2004				A		2005								20040909				
		2004				A		2005						7232				20040		
		2004				A		2005				_	-	7233				20040		
		2004				A		2005						7234				20040		
		2004				A A		2005						7236	0.0		20040909			
		2004:				A		2004 2004						PA88	06		20040910			
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																		20021		
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WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GΙ

$$\begin{array}{c|c}
R^1 & Q = X & R^4 \\
 & & Z & C \\
 & & X \\
 & X \\
 & & X \\$$

AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

IT 603985-87-1P 603985-89-3P 603985-91-7P 603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-87-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 CMF C21 H23 N5 O4

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

<12/04/2007>

Erich Leese

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

$$CH_2-CH_2-N$$
 N
 $C-NH-OH$
 O

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2 10/513699

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PATENT NO.	I	KIND	DATE	APPLICATION NO. DATE	DATE				
CO, GM, LS, PL, UA, RW: GH, KG, FI, BF,	AG, AL, AC, CR, CU, CO, CR, CU, CO, CO, CO, CO, CO, CO, CO, CO, CO, CO	AM, AT, CZ, DE, ID, IL, LV, MA, RU, SC, UZ, VC, LS, MW, RU, TJ, GR, HU, CG, CI,	DK, DM, IN, IS, MD, MG, SD, SE, VN, YU, MZ, SD, TM, AT, IE, IT, CM, GA, 20030918	BA, BB, BG, BR, BY, BZ, CA, CH DZ, EC, EE, ES, FI, GB, GD, GE JP, KE, KG, KP, KR, KZ, LC, LK MK, MN, MW, MX, MZ, NO, NZ, OM SG, SK, SL, TJ, TM, TN, TR, TT ZA, ZM, ZW SL, SZ, TZ, UG, ZM, ZW, AM, AZ BE, BG, CH, CY, CZ, DE, DK, EE LU, MC, NL, PT, RO, SE, SI, SK GN, GQ, GW, ML, MR, NE, SN, TD CA 2003-2476065 2003	CN, GH, LR, PH, TZ, BY, ES, TR,				
AU 20032187			20030922		0311				
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BR 20030076 CN 1639125 CN 1642551 JP 20055253 NZ 534832 CN 10100780 IN 2004DN02 ZA 20040072	24 79 3 537 37 35 32 33 34 36 797 468	A A T A A A A A A A A A A A A A A A A A	RO, MK, 20050111 20050713 20050720 20050825 20050930 20070801 20050928 20051006 20051006 20051006 20051006 20051006 20051006 20050505 20040928	CN 2003-805675 2003 CN 2003-805833 2003 JP 2003-574203 2003 NZ 2003-534832 2003 CN 2007-10005212 2003 IN 2004-DN2537 2004 ZA 2004-7237 2004 ZA 2004-7235 2004 ZA 2004-7232 2004 ZA 2004-7233 2004 ZA 2004-7234 2004 ZA 2004-7236 2004 MX 2004-PA8797 2004 US 2004-507785 2004	20030311 20030311 20030311 20030311 20030311 20030311 20040831 20040909 20040909 20040909 20040909 20040909 20040909				
PRIORITY APPLN.	INFO.:		120.26120	US 2002-363799P P 2002 WO 2002-EP14833 A 2002 CN 2003-805921 A3 2003 WO 2003-EP2515 W 2003	0313 1223 0311				

OTHER SOURCE(S): MARPAT 139:261308

GΙ

$$R^{1}$$
 $Q=X$ N $Z-R^{3}$ R^{4}

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases) 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

RN

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Connection closed by remote host